Pain Reducing Effects of 4-Amino and 4-(1-Piperazinyl) Phenylacetamide Derivatives

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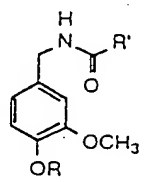
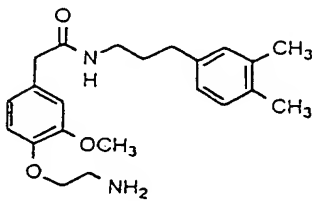
Abstract 4-Aminophenylacetamides were prepared by chemoselective condensation of 4-aminophenylacetic acid and primary amines in the presence of molecular sieves. Conversion to 4-piperazinyl derivatives was accomplished by slight modification of a known method. These new series of 4-amino and 4-(1-piperazinyl)phenylacetamides were evaluated as pain-relieving agents by acetic acid- and PBQ-induced writhing methods after oral administration and proved to have good antiagesic activities.

Analgesics are drugs designed to block the sensation of pain without causing unconsciousness. Much effort has been made to develop analgesics with potency of opioids and without side effects such as psychological and physical dependence as well as tolerance developed by repeated use.[1]



1 R = H, R' = *E*-8-methyl-6-nonenyl

2 R = $CH_2CH_2NH_2$, R' = Z-8-heptadecenyl



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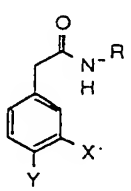

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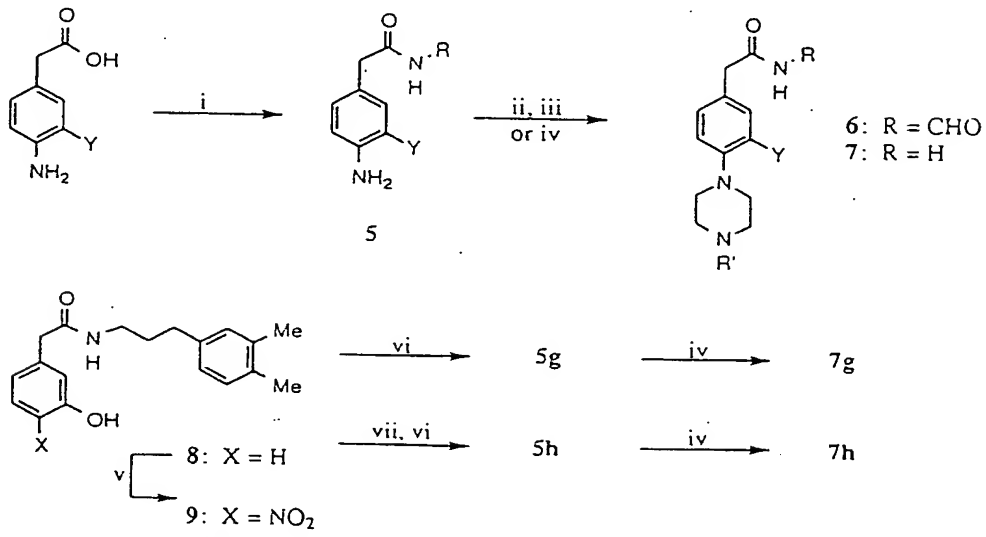
R = alkyl, aralkyl
X = H, OH, OCH_3
Y = NH_2, $N(CH_2CH_2)_2NH$

Since capsaicin (1), a natural product of certain species of the genus *Capsicum*, has been known to have analgesic effects, intensive studies were performed to delineate antinociceptive pathway of capsaicin.[1-4] Due to inherent pungency of capsaicin, synthetic efforts were made to derivatize capsaicin and produced NE-21610 (2) which induced analgesia without initial activation of nociceptors.[5-7] Also, KR-25018 (3) by KRICT proved to be a very potent analgesic agent with decreased pungency compared to capsaicin.[8,9] These structural modifications led to dissociation of analgesia and acute toxicity which has long been thought to be impossible to separate. It is generally believed, though, that the hydroxy and methoxy groups of the aromatic portion of capsaicin are crucial for antinociceptive effect. our recent studies show that 4-amino and 4-piperazinyl derivatives are not so potent as 3 but display diminished side effects at the ED_{50} dosage. Furthermore, preparation of 4-amino derivatives is much simpler and practical. In this paper, we disclose our synthetic studies and pharmacological evaluation of 4-amino derivatives of phenylacetamide as potential analgesic agents.

Chemistry

We began our synthesis of amides 5 by coupling of primary alkyl and aralkylamines with 4-aminophenylacetic acid. The coupling was accomplished in a chemoselctive manner by heating a mixture of an amine and 4-aminophenylacetic acid in the presence of powdered 4 A molecular sieves at 150 °C for 16 - 18 h. This selective amide formation of alkylamine in the presence of arylamine is apparently due to different nucleophilicities. The convenience of this reaction which needs no protection of arylamine moiety

Scheme 1



i) RNH_2, 4 A powdered molecular sieves, 150°C ii) $(ClCH_2CH_2)_2NH{\cdot}HCl$, K_2CO_3, DMF, 160 °C, 12 h
iii) 1 M HCl-MeOH iv) $(ClCH_2CH_2)_2NH{\cdot}HCl$, K_2CO_3, xylene, 150 °C, 24 h
v) HNO_3, H_2SO_4, CH_2Cl_2 vi) H_2, Pd/C vii) CH_3I, K_2CO_3, acetone

makes this process suitable for a large scale production of *N*-alkyl-4-aminophenylacetamides. Conversion of 4-amino group to piperaziane ring was attempted with *bis*(2-chloroethyl)amine hydrochloride and potassium carbonate in *N,N*-dimethylformamide at 155 °C. Interestingly, *N*-formylated compound 6 was formed which was hydrolyzed in methanolic hydrochloric acid to desired 4-(1-piperazinyl)phenylacetamide 7. 7 could be obtained directly from 5 in higher than 80 % yield by changing the solvent to xylene instead of *N,N*-dimethylformamide (Scheme 1, Table 1). The derivatives 5g, 5h, 7g and 7h were prepared from 8 which was generated in 88 % yield by heating 3-hydroxyphenylacetic acid and 3-(3,4-dimethylphenyl)-propylamine in the presence of 4 A powdered molecular sieves. Nitration of 8 to 9 followed by catalytic reduction produced 5g which was transformed to 7g. 5h was also prepared by methylation of 8 followed by hydrogenation. Piperazine ring formation of 5h to 7h was accomplished in a 94 % yield.

Table 1. Synthesis of Phenylacetamides 5 and 7

R-	Y	$X = NH_2$		$X = N(CH_2CH_2)_2NH$	
		Compound	Yield (%)	Compound	Yield (%)
Pentyl	H	5a	73	7a	89
Hexyl	H	5b	76	7b	89
Heptyl	H	5c	66	7c	85
$(CH_2)_3Ph$	H	5d	70	7d	85
$(CH_2)_3$-3-Me-Ph	H	5e	79	7e	-
$(CH_2)_3$-3,4-Me_2-Ph	H	5f	77	7f	90
$(CH_2)_3$-3,4-Me_2-Ph	OH	5g	-	7g	-
$(CH_2)_3$-3,4-Me_2-Ph	OMe	5h	-	7h	94
$(CH_2)_4Ph$	H	5i	70	7i	82

Biological Activity

The analgesic effects of 4-aminophenylacetamides 5a - 5i and 4-(1-piperazinyl)phenylacetamides 7a - 7i were tested by measuring inhibition of writhings induced by acetic acid or phenyl-1,4-benzoquinone (PBQ) administered intraperitoneally.[9] The percentage inhibition of the number of writhing movements (abdominal stretching response) was calculated and the ED_{50} (mg/Kg) value was estimated by regression analysis. The ED_{50} values of the amide 5a - 5i and 7a - 7i are shown in Table 2. Analgesic activities of NE-21610 (2) and other antipyretics are included for comparison. Analgesic effects of 5 and 7 were mainly measured by acetic acid-induced writhing test after oral administration to female ICR mice. These new class of compounds are stronger analgesics than NE-21610 (2). Also, these compounds were tested by PBQ-induced writhing method after oral administration and similar activities were observed compared with those of common antipyretics. Side effects usually displayed by capsaicin, e. g. sedation, vasodilation, ptosis and decrease of respiration, were not observed at the ED_{50} and higher dosages of 5a - 5i and 7a - 7i.

Table 2. Analgesic Effects of Phenylacetamides 5 and 7

Compound	AA (*s. c.*)	AA (*p. o.*)	PBQ (*p. o.*)
NE-21610		>300	35.9
Aspirin			71.4
Ibuprofen			11.0
Phenylbutazone			79.8
5a		>20	
5c		56.8	
5e		7.9	
5f	0.57		
5g			>40
7a		NE	
7b			79
7c		>1.0	
7d			NE
7f		10.9	
7g			13.3
7h			<30
7i		7.1	

AA (*s. c.*): acetic acid-induced writhing method (subcutaneous injection)
AA (*p. o.*): acetic acid-induced writhing method (oral admininstration)
PBQ (*p. o.*): phenylbenzoquinone-induced writhing method (oral admininstration)
Numbers are ED_{50} values in mg/Kg and NE means no effect.

In summary, a new series of phenylacetamide analogs was prepared by chemoselective condensation of 4-aminophenylacetic acid and primary alkyl and aralkylamines. 4-Amino group was converted to 4-(1-piperazinyl) group. This two step process was very efficient with high yields. These 4-amino and 4-(1-piperazinyl) derivatives displayed good analgesic activities by oral administration tested by inhibition of acetic acid or PBQ-induced writhings.

Experimental Section

General. All melting points are uncorrected. ^{1}H-NMR spectra were obtained with Varian Gemini 200 MHz and Bruker AM-300 spectrometers. Reactions were carried out under nitrogen or argon atmosphere. Silica gel used for chromatography was 40 - 63 μm size, as described for flash chromatography.[11] Solvents and reagents were dried and purified prior to use when deemed necessary.

N-(3-Phenylpropyl)-4-aminophenylacetamide (5d). A mixture of 5.00 g (33.1 mmol) of 4-aminophenylacetic acid, 4.90 g (36.4 mmol) of 3-phenylpropylamine, and 3.00 g of powdered 4 A molecular sieve was heated at 150 °C for 16 h and dissolved in 30 mL of dichloromethane. The mixture was directly

purified by flash chromatography (ethyl acetate : hexane = 2 : 1) to give 6.21 g (70 %) of 5d: mp 90 °C; NMR ($CDCl_3$, 300 MHz) δ 1.74 (quint, J = 7.5 Hz, 2H, CH_2), 2.55 (t, J = 7.7 Hz, 2H, CH_2Ar), 3.22 (q, J = 6.8 Hz, 2H, NCH_2), 3.44 (s, 2H, CH_2CO), 3.70 (br s, 2H, NH_2), 5.40 (br t, 1H, NH), 6.67 (m, 2H, ArH), 7.02 (m, 2H, ArH), 7.09 - 7.29 (m, 5H, ArH).

N-(3-Phenylpropyl)-4-(1-piperazinyl)phenylacetamide (7d). A mixture of 1.00 g (3.73 mmol) of 5d, 1.00 g (5.60 mmol) of *bis*(2-chloroethyl)amine hydrochloride, and 2.50 g (18.7 mmol) of potassium carbonate in 30 ml of xylene was heated at 150 °C for 15 h and concentrated in vacuo to remove xylene. The residue was diluted with 100 mL of water and extracted with dichloromethane (100 mL x 2). The combined organic layer was washed with brine, dried, filtered, and concentrated in vacuo. The residue was crystallized in a small amount of dichloromethane - hexane to afford 1.07 g (85 %) of 7d: mp 95 °C; NMR ($CDCl_3$, 300 MHz) δ 1.74 (quint, J = 7.4 Hz, 2H, CH_2), 2.55 (t, J = 7.6 Hz, 2H, CH_2Ar), 3.05 (m, 4H, $2CH_2$), 3.15 (m, 4H, $2CH_2$), 3.22 (q, J = 6.8 Hz, 2H, $CONCH_2$), 3.47 (s, 2H, CH_2CO), 5.38 (br s, 1H, NH), 6.90 (m, 2H, ArH), 7.08 - 7.28 (m, 9H, ArH).

N-Pentyl-4-aminophenylacetamide (5a): mp 86 °C; NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 7.0 Hz, 3H, CH_3), 1.16 - 1.44 (m, 6H, $3CH_2$), 3.17 (q, J = 6.7 Hz, 2H, CH_2N), 3.46 (s, 2H, CH_2CO), 3.67 (br s, 2H, NH_2), 5.39 (br s, 1H, CONH), 6.68 (d, J = 8.3 Hz, 2H, ArH), 7.02 (d, J = 8.3 Hz, 2H, ArH).

N-Hexyl-4-aminophenylacetamide (5b): mp 87 - 88 °C; NMR ($CDCl_3$, 200 MHz) δ 0.85 (t, J = 6.4 Hz, 3H, CH_3), 1.15 -1.41 (m, 8H, $4CH_2$), 3.16 (q, J = 6.7 Hz, 2H, CH_2N), 3.44 (s, 2H, CH_2CO), 3.70 (br s, 2H, NH_2), 5.42 (br s, 1H, NH), 6.65 (d, J = 8.1 Hz, 2H, ArH), 7.01 (d, J = 8.1 Hz, 2H, ArH).

N-Heptyl-4-aminophenylacetamide (5c): mp 91 - 92 °C; NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.7 Hz, 3H, CH_3), 1.15 - 1.45 (m, 10H, $5CH_2$), 3.17 (q, J = 6.7 Hz, 2H, CH_2N), 3.45 (s, 2H, CH_2CO), 3.71 (br s, 2H, NH_2), 5.41 (br s, 1H, NH), 6.67 (d, J = 8.4 Hz, 2H, ArH), 7.12 (d, J = 8.4 Hz, 2H, ArH).

N-{3-(3-Methylphenyl)propyl}-4-aminophenylacetamide (5e): mp 77-79 °C; NMR ($CDCl_3$, 200 MHz) δ 1.65 - 1.82 (quint, J = 7.4 Hz, 2H, CH_2), 2.30 (s, 3H, $ArCH_3$), 2.51 (t, J = 7.7 Hz, 2H, CH_2Ar), 3.20 (q, J = 6.8 Hz, 2H, CH_2N), 3.44 (s, 2H, CH_2CO), 3.70 (br s, 2H, NH_2), 5.37 (br s, 1H, NH), 6.64 - 7.20 (m, 8H, ArH).

N-{3-(3,4-Dimethylphenyl)propyl}-4-aminophenylacetamide (5f): mp 92 - 93 °C; NMR ($CDCl_3$, 300 MHz) δ 1.70 (quint, J = 7.4 Hz, 2H, CH_2), 2.21 (s, 6H, $2CH_3$), 2.48 (t, J = 7.6 Hz, 2H, CH_2), 3.21 (q, J = 6.8 Hz, 2H, CH_2N), 3.44 (s, 2H, NH_2), 5.39 (br s, 1H, NH), 6.65 - 7.26 (m, 7H, ArH).

N-{3-(3,4-Dimethylphenyl)propyl}-3-hydroxyphenylacetamide (8). A mixture of 5.00 g (32.4 mmol) of 3-hydroxyphenylacetic acid, 5.30 g (32.9 mmol) of 3-(3,4-dimethylphenyl)propylamine and 5.0 g of powered 4 A molecular sieves was heated at 150 °C for 5 h. The resulting solid was dissolved in 100 mL of dichloromethane and purified by flash chromatography (ethyl acetate : hexane = 1 : 1) to give 8.49 g (88 %) of 8: mp 92 - 93 °C; NMR ($CDCl_3$, 200 MHz) δ 1.72 (quint, J = 7.4 Hz, 2H, CH_2), 2.21 (s, 6H, $2CH_3$), 2.52

(t, J = 7.6 Hz, 2H, CH_2), 3.24 (q, J = 6.7 Hz, 2H, CH_2N), 3.47 (s, 2H, CH_2CO), 5.56 (br s, 1H, NH), 6.69 - 7.27 (m, 7H, ArH), 7.45 (br s, 1H, OH).

N-{3-(3,4-Dimethylphenyl)propyl}-3-hydroxy-4-nitrophenylacetamide (9). To a solution of 8.00 g (26.9 mmol) of 8 in 150 mL of dichloromethane cooled at 0 °C was added few drops of concentrated sulfuric acid followed by slow addition of 1.0 mL of concentrated nitric acid. The mixture was stirred for 1 h at 0 °C and 2 h at room temperature. The mixture was dissolved in 100 mL of dichloromethane and washed twice with 100-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate : hexane = 1 : 1) to give 3.86 g (42 %) of 9: mp 112 - 114 °C; NMR ($CDCl_3$, 200 MHz) δ 1.84 (quint, J = 7.4 Hz, 2H, CH_2), 2.22 (s, 6H, $2CH_3$), 2.58 (t, J = 7.6 Hz, 2H, CH_2Ar), 3.32 (q, J = 6.6 Hz, 2H, CH_2N), 3.79 (s, 2H, CH_2CO), 5.51 (br t, 1H, NH), 6.71 (dd, J = 2.6, 9.1 Hz, 1H, ArH), 6.86 - 7.06 (m with δ at 6.99, J = 2.6 Hz, 4H, ArH), 8.00 (d, J = 9.1 Hz, 1H, ArH), 10.05 (br s, 1H, OH). An isomeric nitro compound, *N*-{3-(3,4-dimethylphenyl)propyl}-3-hydroxy-6-nitrophenylacetamide, was also obtained: NMR ($CDCl_3$, 200 MHz) δ 1.80 (quint, J = 7.4 Hz, 2H, CH_2), 2.23 (s, 6H, $2CH_3$), 2.55 (t, J = 7.5 Hz, 2H, CH_2Ar), 3.28 (q, J = 6.7 Hz, 2H, CH_2N), 3.49 (s, 2H, CH_2CO), 5.52 (br s, 1H, NH), 6.86 - 6.91 (m, 3H, ArH), 7.03 - 7.06 (m, 2H, ArH), 8.06 (d, J = 8.7 Hz, 1H, ArH).

N-{3-(3,4-Dimethylphenyl)propyl}-4-amino-3-hydroxyphenylacetamide (5g). A mixture of 2.10 g (6.14 mmol) of 9 and 300 mg of 10 % palladium on carbon in 100 mL of ethanol was hydrogenated under 40 psi of hydrogen pressure for 6 h. The mixture was filtered through Celite pad, concentrated in vacuo, and the residue was recrystallized in ethyl acetate - hexane to give 1.59 g (89 %) of 5g: mp 132 - 133 °C; NMR ($CDCl_3$, 200 MHz) δ 1.69 (quint, J = 7.5 Hz, 2H, CH_2), 2.21 (s, 6H, $2CH_3$), 2.46 (t, J = 7.5 Hz, 2H, CH_2Ar), 3.18 (q, J = 6.8 Hz, 2H, CH_2N), 3.37 (s, 2H, $COCH_2$), 5.64 (br s, 1H, NH), 6.50 - 7.03 (m, 6H, ArH).

N-{3-(3,4-Dimethylphenyl)propyl}-4-amino-3-methoxyphenylacetamide (5h). A mixture of 1.60 g (4.68 mmol) of 9, 1.20 g (8.68 mmol) of potassium carbonate and 1.00 mL (16.1 mmol) of iodomethane in 30 mL of acetone was heated at reflux for 3 h and diluted with 200 mL of water, followed by extraction with two 200-mL portions of dichloromethane. The combined organic layer was dried ($MgSO_4$), and concentrated in vacuo to give a quantitative yield of *N*-{3-(3,4-dimethylphenyl)-propyl}-3-methoxy-4-nitrophenylacetamide: mp 89 - 90 °C; NMR ($CDCl_3$, 200 MHz) δ 1.72 (quint, J = 7.4 Hz, 2H, CH_2), 2.22 (s, 6H, $2CH_3$), 2.55 (t, J = 7.5 Hz, 2H, CH_2Ar), 3.28 (q, J = 6.7 Hz, 2H, CH_2), 3.53 (s, 2H, CH_2CO), 3.95 (s, 3H, OCH_3), 5.51 (br s, 1H, NH), 6.84 - 7.04 (m, 5H, ArH), 7.82 (d, J = 8.3 Hz, 1H, ArH).

A mixture of the crude amide and 400 mg of 10 % palladium on carbon in 50 mL of ethanol was hydrogenated under 40 psi hydrogen pressure for 6 h. The mixture was filtered through Celite pad, concentrated in vacuo, and the residue was recrystallized in ethyl acetate - hexane to give 1.31 g (90 % overall) of 5h: mp 101 - 102 °C; NMR ($CDCl_3$, 200 MHz) δ 1.71 (quint, J = 7.4 Hz, 2H, CH_2), 2.22 (s, 6H, $2CH_3$), 2.49 (t, J = 7.7 Hz, 2H, CH_2), 3.21 (q, J = 6.6 Hz, 2H, CH_2N), 3.46 (s, 2H, CH_2CO), 3.84 (s, 3H, OCH_3), 5.44 (br s, 1H, NH), 6.61 - 7.04 (m, 6H, ArH).

N-(4-Phenylbutyl)-4-aminophenylacetamide (5i): mp 63 °C; NMR ($CDCl_3$, 300 MHz) δ 1.38 - 1.61 (m, 4H, $2CH_2$), 2.58 (t, J = 7.4 Hz, 2H, CH_2Ar), 3.20 (q, J = 6.6 Hz, 2H, NCH_2), 3.45 (s, 2H, CH_2CO), 3.69 (br s, 2H, NH_2), 5.38 (br t, 1H, NH), 6.66 (m, 2H, ArH), 7.00 (m, 2H, ArH), 7.12 - 7.30 (m, 5H, ArH).

N-Pentyl-4-(1-piperazinyl)phenylacetamide (7a): mp 124 °C; NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 7.0 Hz, 3H, CH_3), 1.14 - 1.28 (m, 4H, $2CH_2$), 1.40 (quint, J = 7.2 Hz, 2H, CH_2), 2.12 (br s, 1H, NH), 3.10 (m, 4H, $2NCH_2$), 3.19 (m, 6H, $3NCH_2$), 3.46 (s, 2H, CH_2CO), 5.36 (br t, 1H, CONH), 6.90 (d, J = 8.7 Hz, 2H, ArH), 7.14 (d, J = 8.7 Hz, 2H, ArH).

N-Hexyl-4-(1-piperazinyl)phenylacetamide (7b): mp 123 - 125 °C; NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.8 Hz, 3H, CH_3), 1.23 (m, 6H, $3CH_2$), 1.38 (quint, J = 6.9 Hz, 2H, CH_2), 3.07 (m, 4H, $2NCH_2$), 3.17 (m, 6H, $3NCH_2$), 3.49 (s, 2H, CH_2CO), 5.37 (br t, 1H, NH), 6.90 (d, J = 8.7 Hz, 2H, ArH), 7.13 (d, J = 8.6 Hz, 2H, ArH).

N-Heptyl-4-(1-piperazinyl)phenylacetamide (7c): mp 102 - 104 °C; NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 6.8 Hz, 3H, CH_3), 1.16 - 1.45 (m, 10H, $5CH_2$), 3.02 - 3.21 (m, 10H, $5NCH_2$), 3.49 (s, 2H, CH_2CO), 5.40 (br s, 1H, NH), 6.91 (d, J = 8.7 Hz, 2H, ArH), 7.13 (d, J = 8.7 Hz, 2H, ArH).

N-{3-(3,4-Dimethylphenyl)propyl}-4-(1-piperazinyl)phenylacetamide (7f): mp 118 - 122 °C; NMR ($CDCl_3$, 300 MHz) δ 1.71 (quint, J = 7.3 Hz, 2H, CH_2), 2.21 (s, 6H, $2CH_3$), 2.48 (t, J = 7.7 Hz, 2H, CH_2Ar), 3.02 - 3.17 (m, 8H, $4NCH_2$), 3.20 (q, J = 6.7 Hz, 2H, NCH_2), 3.47 (s, 2H, CH_2CO), 5.38 (br s, 1H, NH), 6.81 - 7.13 (m, 7H, ArH).

N-{3-(3,4-Dimethylphenyl)propyl}-3-hydroxy-4-(1-piperazinyl)phenylacetamide (7g): mp 113 - 117 °C; NMR ($CDCl_3$, 200 MHz) δ 1.72 (quint, J = 7.2 Hz, 2H, CH_2), 2.20 (s, 6H, $2CH_3$), 2.48 (t, J = 7.7 Hz, 2H, CH_2), 2.83 (m, 4H, $2NCH_2$), 3.03 (m, 4H, $2NCH_2$), 3.19 (q, J = 6.7 Hz, 2H, CH_2NCO), 3.45 (s, 2H, CH_2), 5.42 (br s, 1H, NH), 6.67 - 7.13 (m, 7H, ArH).

N-{3-(3,4-Dimethylphenyl)propyl}-3-methoxy-4-(1-piperazinyl)phenylacetamide (7h): NMR ($CDCl_3$, 200 MHz) δ 1.70 (quint, J = 7.5 Hz, 2H, CH_2), 2.19 (s, 6H, $2CH_3$), 2.47 (t, J = 7.5 Hz, 2H, CH_2), 2.65 (m, 4H, $2NCH_2$), 3.16 (m, 6H, $3NCH_2$), 3.47 (s, 2H, CH_2CO), 3.82 (s, 3H, OCH_3), 4.96 (br s, 1H, NH), 5.37 (br t, 1H, CONH), 6.71 - 7.03 (m, 6H, ArH).

N-(4-Phenylbutyl)-4-(1-piperazinyl)phenylacetamide (7i): mp 113 - 114 °C; NMR ($CDCl_3$, 200 MHz) δ 1.37 - 1.65 (m, 4H, $2CH_2$), 2.58 (t, J = 7.3 Hz, 2H, CH_2Ph), 3.02 - 3.28 (m, 10H, $5NCH_2$), 3.48 (s, 2H, CH_2CO), 5.37 (br s, 1H, NH), 6.89 - 7.32 (m, 9H, ArH).

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References

1. Garnder, J. H.; Kasting, G. B.; Cupps, T. L.; Echler, R. S.; Gibson, T. W., EP 0,282,127 (1988).
2. Suzuki, T.; Iwai, K. The Alkaloids, Academic Press, 1984, vol XXIII, p 227.
3. Thresh, J. C., *Pharm. J. Trans.* 1976, *7*, 21, 259, 473.
4. Chudaponse, P.; Janthasoot, J., *Biochem. Pharmacol.* 1981, *30*, 735.
5. Nopanitaya, W.; Nye, S. W., *Toxicol. Appl. Pharmacol.* 1974, *30*, 149.
6. Glinsukon, T.; Stitmunnaithum, V.; Toskulkao, C.; Burannuti, T.; Tangkrisanavinont, V., *Toxicon.* 1980, 18, 215.
7. Dray, A.; Batterby, J.; Rueff, A.; Walpole, C.; Wrigglesworth, R. *European J. Pharm.* 1990, *181*, 289.
8. Park, N.-S.; Ha, D.-C.; Kim, H.-S.; Choi, J.-K., *Kor. J. Med. Chem.* 1991, *1*, 2.
9. Park, N.-S.; Ha, D.-C.; Choi, J.-K.; Kim, H.-S.; Lim, H.-J.; Lee, B.-Y., *Kor. J. Med. Chem.* 1991, *1*, 36.
10. Cossy. J; Pale-Grosdemange, C. *Tetrahedron Lett.*, 1989, *30*, 2771.
11. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, 1978, *43*, 2923.